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Prostate specific antigen patterns in US and European populations: comparison of six diverse cohorts

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Abstract

Objective: To determine whether there are differences in prostate specific antigen (PSA) at diagnosis or changes in PSA between US and European populations of men with and without prostate cancer.

Subjects and methods: Repeated measures of PSA from six clinically and geographically diverse patient cohorts: two cohorts of men with PSA-detected prostate cancer, two cohorts with clinically-detected prostate cancer and two cohorts of men without prostate cancer. Using multilevel models, average PSA at diagnosis and PSA change over time were compared between populations.

Results: Annual percentage PSA change of 4-5% was similar between men without cancer and men with PSA-detected cancer. PSA at diagnosis was 1.7ng/ml lower in a US cohort of PSA-detected men (95% CI 1.3-2.0ng/ml), compared to a PSA-detected UK cohort, but there was no evidence for a different rate of PSA change between these populations.

Conclusion: PSA changes over time are similar in UK and US men diagnosed through PSA testing and even in men without prostate cancer. Further development of PSA models to monitor men on active surveillance should be undertaken in order to take advantage of these similarities. We found no evidence that guidelines for using PSA to monitor men cannot be passed between US and European studies.

1. Introduction

Active surveillance (AS) is increasingly being used as an alternative to immediate radical intervention for men with localised prostate cancer, at low risk of progressing to life threatening disease(1-3). As radical treatment comes with a risk of harm(4), there is strong motivation to intervene in only those men with a high risk of disease progression. Circulating prostate specific antigen (PSA) has been used as a biochemical measure of prostate cancer for many years. AS commonly includes regular measurement of PSA, with increasing values used as a trigger for review. If signs of disease progression are found on clinical review, there is the opportunity for radical intervention before the opportunity for cure has passed.

Dynamic measures of PSA, such as PSA doubling time and PSA velocity are used by several AS studies to alert clinicians to rapidly rising PSA(5). Furthermore, PSA levels increase naturally with age, and methods are being developed to indicate when increases in PSA are beyond normal age-related(6-9). However, there is currently no evidence on whether there is common PSA change in men with localised prostate cancer in different populations. Although AS studies are beginning worldwide, the larger, more mature cohorts are based in Europe and North America(10). Differences in the effect of PSA screening have been suggested between these populations(11, 12), although there are several flaws with this interpretation(13). Nevertheless, the American Medical Association recommends annual screening after age 55 in the US(14), while no such recommendations exist in Europe.

This could lead to different populations of men with prostate cancer in the US (e.g. detected at an earlier stage), who then may or may not have similar PSA kinetics to their European counterparts. Thus it is unclear whether longitudinal PSA changes may differ in men on AS.

Monitoring protocols and triggers for clinical review are being devised to suit all men on AS without requiring recalibration to each new population. It is therefore crucial to investigate these differences and to adjust PSA protocols if necessary. Further, if PSA change is found to be similar on average in men with and without prostate cancer then, for a future individual, it may be possible to separate normal age-related change in PSA from pathologically influenced changes which are a symptom of more aggressive cancer.

To this end, this article provides comparisons of (i) PSA change in men with and without prostate cancer; (ii) PSA change in men with prostate cancer who were detected clinically or through a PSA test; and (iii) PSA change in UK and US men in modern AS studies.

2. Methods

2.1 Study Populations

Data were available from ongoing AS studies based at the Royal Marsden(15) and Johns Hopkins(16) hospitals. The Royal Marsden data include 492 men and 9243 PSA tests (obtained between 1999 and 2012) while the Johns Hopkins data comprises 6352 PSA test results from 994 men (obtained between 1993 and 2012). In most men diagnosis was based on a raised PSA value and subsequent positive biopsy, so this represents a modern AS cohort.

The Scandinavian Prostate Cancer study Group 4 (SPCG4) cohort analysed here contains 198 men and 2120 PSA tests(17), and the University of Connecticut Health Centre (UCHC) cohort consists of 101 men and 775 PSA test results(18, 19). In both cohorts, men were diagnosed with localised prostate cancer between 1989 and 1993 and represent a population whose disease was likely detected at a later stage than in the PSA era, in the most part through clinical presentation with symptoms, or incidentally during treatment for urological conditions.

Two cohorts of men without prostate cancer were also included to examine differences in PSA change between men with and without cancer. Data from the Baltimore Longitudinal Study of Aging (BLSA)(20) contained 5012 PSA measurements from 1032 men without prostate cancer. A model for PSA change in 1432 men without cancer from the Krimpen study(21, 22) (a large prospective community-based study in the Netherlands) has appeared elsewhere(8), and the coefficients from this model are presented here for comparison.

PSA was collected for a variety of reasons among these six cohorts (Table 1), and the differences between these could lead to biases in modelling these PSAs together. However,

all were measured on men who were untreated for prostate cancer, i.e. these were `natural' observations of PSA in later life in several thousand men.

2.2 Comparing PSA change between men with and without prostate cancer

In each of the five cohorts (Royal Marsden, Johns Hopkins, SPCG4, UCHC and BLSA), we modelled repeated measures of PSA using a separate multilevel model (with a random intercept and slope). In each model, we log transformed PSA values to account for the skewed distribution of PSA. The intercept and slope of these models are presented to compare the average PSA level at 50 (age was centred at 50 in each model to correspond to the Krimpen model(22), and because there is no age at diagnosis for Krimpen or BLSA) and percentage change in PSA value per year from 50-80 (the maximum age in the data) respectively. These models have previously been applied to the Krimpen study(22), so here we can compare change in PSA levels between six cohorts: two from men without prostate cancer (BLSA and Krimpen); two from the clinically detected era of prostate cancer (SPCG4 and UCHC); and two from the modern PSA-detected era of prostate cancer (Royal Marsden and Johns Hopkins).

2.3 Comparing PSA trends between PSA detected men and clinically detected men with prostate cancer

Log transformed PSA data from the four prostate cancer cohorts were combined and a multilevel model was fit to these data, including an interaction term between cohort and age, so that a comparison of PSA change could be made. This model also included Gleason score at diagnosis (3+3, 3+4 or 4+3) and its interaction with age, so that we could further compare whether Gleason score had an association with average PSA level or PSA change. Time from diagnosis, rather than age, was used as the time-varying covariate to allow for

interpretation of the intercept as the average estimated PSA value at diagnosis. To correct for different ages of men in the studies, we controlled for age at diagnosis in the models. Within subject variation was allowed to be different in each study, to improve model fit, and this is reported as a measure of the natural variation of PSA levels over time for men in each cohort.

3. Results

Table 2 summarises the PSA data in each of the six cohorts. On average, the SPCG4 cohort has the highest average PSA value at diagnosis (8.9ng/ml) while the UCHC cohort has the oldest cohort at diagnosis (69.8 years). The Royal Marsden and UCHC cohorts are similar in terms of diagnostic PSA and follow-up time, but there are many more PSA tests per person in the more modern Royal Marsden cohort. Johns Hopkins has the lowest average PSA at diagnosis (5.0ng/ml) and shortest follow-up time (3.5 years), yet has the most men on surveillance (994) among the cancer cohorts. There was a similar proportion of Gleason 3+3 men in the modern AS cohorts (91% in RMH, 95% in Johns Hopkins), but this was lower in UCHC (75% 3+3 men) and SPCG4 (67% 3+3 men).

3.1 Comparing PSA change between men with and without prostate cancer

Men on surveillance and men without prostate cancer have similar age-related PSA change (Table 3). For example, the average PSA change per year is very similar in the Krimpen, BLSA, Royal Marsden and Johns Hopkins cohorts, with a 4- 5% increase in PSA per year. Men in the older, clinically detected cohorts have a much steeper rate of change, increasing by 7% and 14% per year in UCHC and SPCG4 respectively.

The left panel of Figure 1 shows a PSA curve for a hypothetical man in each cohort who has a PSA value of 2ng/ml at age 50. This graph is used to show the similarities of the four modern cohorts, whether they involve men with or without prostate cancer. However, the results from the multilevel models suggest that men without cancer have much lower average PSA values at age 50 – both have an average estimated PSA value below 1ng/ml. In the right panel of Figure 1, the estimated average PSA level at age 50 is much lower in the Krimpen and BLSA cohorts. However, since only men with raised PSA levels are biopsied, the

disease status of men in these cohorts is unclear. The low average PSA value estimate at age 50 for the clinically detected men (SPCG4 and UCHC) is a result of extrapolating below the ages of men in these two cohorts.

3.2 Comparing PSA trends between men with PSA-detected and clinically detected prostate cancer

The combined model included 1855 men and 18645 repeated measures of PSA (average 10 per person, range 1 to 54), results are shown in Table 4. The Royal Marsden men with Gleason score 3+3 provided the largest amount of PSA data and were used as the reference group. They had mean PSA value at diagnosis of 5.56ng/ml (95% CI 5.21-5.93ng/ml) with a PSA change of 5.7% per year (95% CI 4.3-7.1%). Both US cohorts had a lower PSA value at diagnosis than the UK AS study, with PSA level at diagnosis estimated as 3.93ng/ml in Johns Hopkins (95% CI 3.63, 4.25ng/ml) and 4.24ng/ml in UCHC (95% CI 3.60-5.00ng/ml). However, there was no strong evidence for a difference in the rate of change of PSA between UK and US populations, with PSA increasing by 5.7% (95% CI 4.3-7.1%) and 5.9% (95% CI 4.1-7.8%) in Royal Marsden and Johns Hopkins respectively. Men in the SPCG4, clinically detected, cohort had a higher PSA value at diagnosis on average (8.54ng/ml, 95% CI 7.64-9.55) and a higher rate of PSA change per year (17.3%, 95% CI 14.5-20.1%) compared with the Royal Marsden AS men.

Men with Gleason scores 3+4 (6.26ng/ml, 95% CI 5.73, 6.83ng/ml) and 4+3 (9.67ng/ml, 95% CI 6.60, 14.17ng/ml) had higher PSA value at diagnosis than Gleason 3+3 men (5.56, 95% CI 5.21, 5.93). There was also evidence that men with Gleason score 4+3 (23.1% increase per year, 95% CI 10.9, 36.7%) had a higher rate of PSA change compared to Gleason 3+3 men (5.7% increase per year, 95% CI 4.3, 7.1%). The within subject variation in PSA level was

higher in the older, clinically detected cohorts, with an average variation of 0.324ng/ml (95% CI 0.314, 0.335ng/ml) and 0.404ng/ml (95% CI 0.383, 0.426ng/ml) in the SPCG4 and UCHC cohorts respectively, compared to 0.270ng/ml (95% CI 0.266, 0.274ng/ml) in Royal Marsden and 0.261ng/ml (0.255, 0.266ng/ml) in the Johns Hopkins cohort.

4. Discussion

Longitudinal PSA changes over time were similar between men without prostate cancer (BLSA and Krimpen cohorts) and men with cancer detected by a PSA test (Royal Marsden and Johns Hopkins cohorts), with PSA values rising by between 4 and 5% per year between the ages of 50 and 80. However, men without cancer had lower average PSA levels estimated at 50 years. In clinically detected men, the rate of increase was higher - between 7% (UCHC) and 14% (SPCG4) per year. A more in-depth comparison of the prostate cancer cohorts suggested that the average PSA level at diagnosis was 1.6ng/ml lower in US compared to UK populations, and 3ng/ml higher at diagnosis in clinically detected European men, compared with PSA-detected UK men. We found no strong evidence for PSA change differences between modern AS men in the US and UK populations. However, clinically detected men (SPCG4) had an 11.5% per annum higher rate of PSA change, compared with modern AS men in the UK. The Royal Marsden (Europe-PSA) and UCHC (USA-symptomatic) are similar in baseline and overall PSA. This suggests that while PSA at diagnosis is likely lower in the US (perhaps due to repeat PSA testing), PSA change is similar between modern AS populations.

We also find that men with more aggressive cancer (Gleason score 4+3), have much higher rates of PSA increase than men with Gleason score 3+3. This suggests PSA may be useful as a biomarker in more aggressive cancer, while in the majority of lower grade tumours, PSA change is comparable to men without cancer. The change in PSA in the Gleason 4+3 men is 23% per year (95% CI 11-37%) and there is strong evidence in other studies that higher Gleason score is associated with increased mortality(23). However, without any clinical

outcomes such as metastases, no strong conclusions can be made here for the clinical utility of PSA.

In order to use PSA in AS, a model for "normal" PSA levels is needed, as a comparator for observed PSA levels in men on AS. From Table 5 it is evident that PSA doubling time, PSA velocity and absolute level of PSA are commonly used measures for monitoring a man's PSA level(5, 24, 25). There is little consensus on which of these to use or what threshold should be employed for each measure. There remains an absence of clinical or statistical evidence for their use in active monitoring, and retrospective analyses have found very little association with clinical outcomes such as metastases or prostate cancer specific mortality(5, 26-29). Furthermore there are concerns about the various methods of calculation of PSA doubling time(30, 31) and PSA velocity(32, 33) as well as a great deal of variation and uncertainty about how many PSA values should be used for calculation(7). PSA levels increase naturally with age, so that a method is needed to indicate when increases in PSA are beyond normal age-related change, to avoid reviews being triggered when they are not necessary.

It has recently been suggested that a single early PSA test (around age 40-55) might be used to determine aggressive prostate cancer in later life(34). A similar test early in AS may also be useful in determining the frequency of PSA monitoring during AS. Answering this question is beyond the scope of the current analysis, and would require AS studies with enough clinical events (e.g. metastases) to distinguish PSA trends between fatal and non-fatal prostate cancers. Some work on this topic has recently appeared(35), suggesting that not enough clinical events are currently available to perform such an analysis.

Strengths of this study include the large amount of data available for model development and validation, with the combined model using data from 1855 men and 18645 PSA tests. Our data come from both the US and UK populations and traverse two eras of prostate cancer detection: the symptomatic presenting man from the early 1990s and the PSA-detected man of the 2000s. The follow-up periods for these men were relatively long, with 3.5, 4.4, 4.7 and 6-year averages for the prostate cancer cohorts. It was also very important to have Gleason score available for each cohort, so this could be investigated alongside cohort effects.

One limitation of this work is censoring by treatment in the modern AS cohorts. In both Royal Marsden and Johns Hopkins, men with rapidly rising PSA are more likely to receive treatment than men with stable PSA, due to triggers for clinical review which involve PSA(10, 16, 36), although we did not have any data on whether a man has left AS due to censoring by treatment, death or end of study. This may explain the differences between the UCHC and SPCG4 cohorts. For example, in UCHC there may have been more sensitive PSA criteria for clinical review, such that men with rapidly rising PSA are not included in the available data, whereas in SPCG4 they are included. Selection bias may have been introduced by the different populations of men being included in the combined analysis. Inclusion criteria and triggers to leave surveillance were different between the four cohorts of men with prostate cancer, and they were diagnosed by different means (PSA tests vs clinically presenting with symptoms). Men in SPCG4 were randomised as part of an RCT to follow a conservative management approach, while men in Johns Hopkins, Royal Marsden and Connecticut all were recruited to active surveillance programs after a diagnosis of clinically localised prostate cancer. However, the PSA data from these four cohorts come from men with untreated, clinically localised prostate cancer. From Table 5 it is evident that

differences in AS eligibility, monitoring and triggers to leave surveillance remain diverse. Thus, using these large datasets while controlling for study provides best possible comparison of PSA change between populations.

The evidence provided here, namely that PSA change is similar in contemporary cohorts of AS with and without localised prostate cancer in both Europe and the US, suggests that models for PSA change could be developed for use in monitoring studies. For instance, PSA doubling time and PSA velocity are currently calculated for each man separately and compared to fixed thresholds (e.g. PSA doubling time < 3 years is used by several studies(10)). If PSA change is similar between populations, a database of PSA change could be established, such that comparisons of an individual's PSA doubling time with other similar men could be made. These comparisons may be more useful at determining abnormal PSA doubling time, than comparing with a fixed threshold. Indeed, as more and more men are entered into AS studies, this collection of data would be continually strengthened, leading to improved ability to pick out adverse changes in PSA during monitoring.

National Institute for Health and Care Excellence(37) guidelines suggest monitoring men on AS using PSA kinetics. Since the large US and Canadian studies drive the thresholds used to make clinical decisions (e.g. PSA doubling time < 3 years used in a large Toronto study(38) has been adopted by the largest ongoing AS study, PRIAS(39)), it is important to see whether clinicians in the UK and Europe should base their PSA kinetic decisions on these thresholds. We find little evidence for a difference in PSA change during follow-up between US and UK men, which suggests that using thresholds from the large US and Canadian studies is appropriate in other populations.

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Conflict of interests

None reported

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Abbreviations

AS = active surveillance; BLSA = Baltimore Longitudinal Study of Aging; CI = confidence interval; PSA = prostate specific antigen; SPCG4 = Scandinavian Prostate Cancer study Group 4; UCHC = University of Connecticut Health Center

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Table 1: Description of the studies used for analysis of PSA trends

Cohort	RMH	JH	UCHC	SPCG4	BLSA	Krimpen
Circumstances of PSA collection	Ongoing prospective active surveillance study(36)	Ongoing prospective active surveillance study(16)	Prospective active surveillance study(19)	Randomised controlled trial of watchful waiting against radical prostatectomy. PSA collected on men in the WW arm of the RCT(17)	Ongoing prospective study of aging and PSA(20)	Prospective study of aging and PSA(21, 22)
Years of diagnosis	1999-2010	1992-2012	1990-1993	1989-1999	n/a	n/a
Years of PSA testing	1999-2012	1992-2012	1990-2005	1989-2005	1990-2012	1995-2004
Inclusion criteria	Baseline PSA < 15ng/ml; Gleason score ≤ 3+4; T2; % positive biopsy cores ≤ 50%	PSA density < 0.15ng/ml/cm^3; Gleason score ≤ 3+3; T1c; two or less positive biopsy cores; maximum involvement of 50% per core	Age<75, Baseline PSA < 10ng/ml; Gleason ≤ 6; 1-2 cores + <50% in any single core	Age < 75; T0d, T1, or T2; life expectancy > 10 years.	Age: 20-97, no prior diagnosis of prostate cancer. Men with a diagnosis of prostate cancer during follow-up, were censored	Age: 50-78, no prior diagnosis of prostate cancer. Men with a diagnosis of prostate cancer during follow-up, were censored
Monitoring schedule	PSA tests every 3-4 months in the first 2 years then every 6 months	PSA tests every 6 months	PSA tests every 6 months. If trending upward, every 3 months	PSA tests every 6 months for two years and annually thereafter	Every 1 to 4 years depending on age	Baseline PSA tests and subsequent follow-up tests after an average of 2.1, 4.2 and 6.5 years

Table 2: Descriptive statistics for each cohort

Study	Description	Cohort size	PSA tests	Median tests per individual	Average follow-up (st. dev.)	Average age at first PSA (st. dev.)	Average first PSA, ng/ml (st. dev.)	Gleason grade (%)
Krimpen (Netherlands)	Men without PCa	1462	3353	3	4.2	61.1 (6.6)	1.7 (1.8)	n/a
BLSA (USA)	Men without PCa	1032	5012	3	13.2 (10.9)	52.0 (16.1)	1.42 (2.7)	n/a
Royal Marsden (UK)	Men with localised PCa on AS	492	9243	19	4.4 (2.6)	65.7 (6.2)	6.90 (3.5)	3+3 (91%) 3+4 (8%) 4+3 (1%)
Johns Hopkins (USA)	Men with localised PCa on AS	994	6352	5	3.5 (2.8)	65.7 (6.1)	4.96 (2.8)	3+3 (95%) 3+4 (5%) 4+3 (0%)
SPCG4 (Sweden)	Men with clinically detected PCa, on WW	198	2120	11	6.0 (3.8)	67.2 (5.7)	8.91 (5.1)	3+3 (67%) 3+4/4+3 (33%)
UCHC (USA)	Men with clinically detected PCa, on WW	101	775	6	4.7 (3.9)	69.8 (4.5)	6.66 (4.4)	3+3 (75%) 3+4 (11%) 4+3 (14%)

AS = active surveillance, PCa = prostate cancer, WW = watchful waiting

Table 3: Coefficients from linear multilevel models for log(PSA) change in each of six cohorts

	Men without prostate cancer		**Men with prostate cancer**			
Cohort	Krimpen(21)	BLSA	Royal Marsden	JH	SPCG4	UCHC
Estimated PSA value at age 50 (ng/ml)	0.73	0.65	2.55	2.08	1.10	1.23
Percentage change in PSA per year in age (%)	4.54	4.14	4.68	4.15	14.0	7.10

Table 4: Results from a multilevel model of repeated log(PSA) data, including data from all four prostate cancer cohorts

Parameter	Category	Coefficient	95% confidence interval	p-value for difference between categories
Average PSA value at diagnosis	***Royal Marsden***	5.56ng/ml	5.21, 5.93ng/ml	p<0.0005
	Johns Hopkins	3.93ng/ml	3.63, 4.25ng/ml	
	SPCG4	8.54ng/ml	7.64, 9.55ng/ml	
	UCHC	4.24ng/ml	3.60, 5.00ng/ml	
Change in PSA per year	***Royal Marsden***	5.72%	4.31, 7.14%	p<0.0005
	Johns Hopkins	5.92%	4.05, 7.81%	
	SPCG4	17.31%	14.56, 20.12%	
	UCHC	5.68%	1.92, 9.58%	
Average PSA value at diagnosis by Gleason score	***3+3***	5.56ng/ml	5.21, 5.93ng/ml	p<0.0005
	3+4	6.26ng/ml	5.73, 6.83ng/ml	
	4+3	9.67ng/ml	6.60, 14.17ng/ml	
Change in PSA per year by Gleason score	***3+3***	5.72%	4.31, 7.14%	p=0.0042
	3+4	7.53%	5.31, 9.81%	
	4+3	23.11%	10.85, 36.72%	
Average increase in PSA per year of age at diagnosis		1.53%	0.96, 2.11%	
PSA residual standard deviation by study	***Royal Marsden***	0.270ng/ml	0.266, 0.274 ng/ml	p<0.0005
	Johns Hopkins	0.261ng/ml	0.255, 0.266 ng/ml	
	SPCG4	0.324ng/ml	0.314, 0.335 ng/ml	
	UCHC	0.404ng/ml	0.383, 0.426 ng/ml	

Table 5: Description of the use of PSA for eligibility, monitoring and triggering clinical review in large AS studies

Setting	PSA eligibility	PSA monitoring	PSA trigger for clinical review	Sample size (years recruited)
Memorial Sloan Kettering Cancer Centre, New York, USA(41)	<10	every 6 mo.	PSA ≥ 10ng/ml	238 (1993-2009)
University of Miami, USA(42)	≤10	every 3-4 mo. for 2 yrs, then every 6 mo.	No defined PSA trigger	276 (1994-2011)
University of Toronto, Canada(38)	≤10 2000 - ≤15 1995-1999	every 3 mo. for 2 yrs, then every 6 mo. for stable patients	PSADT < 3 yrs	450 (1995-2010)
ERSPC, Gothenburg, Sweden(43)	<10 (low risk gp.) < 20 (inter risk gp.)	every 3-6 mo.	"Established PSA progression"	439 (1995-2010)
UC, San Francisco, USA(44)	within CAPRA score	every 3 mo.	PSADT ≤2yrs	466 (1995-2010)
Johns Hopkins University, USA(16)	PSA density < 0.15ng/ml/cc	every 6 mo.	PSA density ≥ 0.15/ml/cc	769 (1995-2011)
Royal Marsden NHS Trust, UK(45)	<15	every 3 mo. in 1st yr, every 4 mo. in 2nd yr, every 6 mo. after 2 yrs	PSAv>1ng/ml/yr,	471 (2002-2011)
PRIAS (International), Rotterdam based, Holland(39)	≤10 ; PSAD<0.2ng/ml/cc	every 3 mo. for 2 yrs, then every 6 mo.	PSADT < 3yrs	2494 (2006-2012)

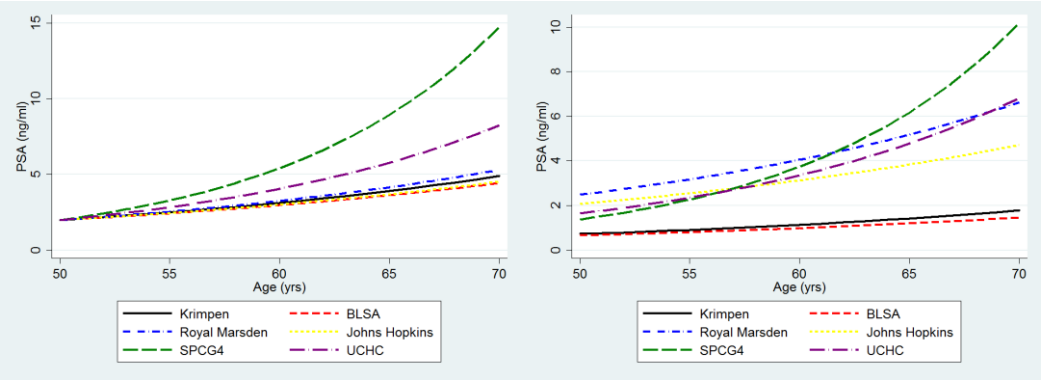

Figure 1: PSA change in the six cohorts: change for a man with an initial PSA at age 50 of 2ng/ml (left); change using actual estimated PSA at age 50 (right)